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The place of initial serum sodium and globulin ratio in the prognosis estimation of patients with lung cancer

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ABSTRACT

Aims: Since lung cancer is a disease with a high mortality and morbidity rate, determining its prognosis has a very important place. Studies in the literature have shown that electrolyte disturbance and inflammation may be associated with a poor prognosis in lung cancer, however, further studies are needed on this subject. In this study, it was planned to investigate the role of the sodium and globulin ratio measured at the time of diagnosis in the prognosis prediction of patients with lung cancer diagnosis.

Methods: The study was carried out retrospectively from the patient files and hospital records of 165 patients who were followed up with the diagnosis of lung cancer between January 1, 2015 and January 1, 2021 in Kırıkkale University (KKU) Faculty of Medicine, Department of Internal Medicine, and Medical Oncology Department. Patients with achievable sodium, albumin, and total protein values at the time of diagnosis were included in the study. The hemogram parameters of the patients included in the study were creatinine and estimated glomerular filtration rate (eGFR), alanine aminotransferase (ALT) level, albumin level, total protein level and globulin level, C-reactive protein (CRP) level, CEA, and TSH levels. In addition, the sodium/globulin ratio (SGR) and the CRP/albumin ratio (CAR) were evaluated.

Results: 87.3% of the patients were male, and 12.7% were female. The mean age at presentation was 62.5±9.1 years. Adenocancer accounts for 46.1% of cancers with 76 patients, squamous cell carcinoma for 41.8% with 69 patients, and small cell carcinoma for 12.1% with 20 patients. 11 (6.7%) of the patients were stage 1, 25 (15.2%) stage 2, 58 (35.2%) stage 3, and 71 (43%) stage 4 patients. 111 (67.3%) of the patients died. The average follow-up time is 16.6 months. In the regression analyzes performed in our study, mortality and sodium/globulin ratio (SGR) and progression-free survival and sodium/globulin ratio (SGR) were found to be unrelated. There was a weak negative correlation between the sodium/globulin ratio (SGR) and the CRP/albumin ratio (CAR). In the multivariate regression analysis, the stage of the disease, diabetes, and CRP level were found to be the independent variables affecting mortality and the stage of the disease affecting progression-free survival. ($p<0.001$).

Conclusion: Independent prognostic factors in patients with lung cancer; stage of disease for mortality, diabetes, and CRP level were found to be stages for progression-free survival. Considering the weak relationship between sodium/globulin ratio (SGR) and CRP/albumin ratio (CAR), SGR can be used as a future biomarker to predict prognosis in cancer patients. Further studies are needed to learn more about the relationship between SGR and lung cancer.

Keywords: Lung cancer, sodium, globulin, overall survival, mortality

INTRODUCTION

Lung cancer is the leading cause of cancer-related death in the world.[1] It is one of the diseases with high mortality and morbidity rates worldwide due to the increase in smoking rates in the population. The average life expectancy for lung cancer is 1 year, and the 5-year survival rate has been reported to be 19%. Therefore, lung cancer constitutes one of the biggest health problems in the world.[2]

Inflammation and the tumor microenvironment are factors in the development and progression of cancer.[3] Cells involved in the mechanism of inflammation may be influential factors in cancer formation, tumor progression, and patient survival.[3,4] Inflammation is often associated with the development and progression of cancer. Therefore, targeting the suppression of inflammation represents an important strategy for both cancer prevention and cancer treatment.[5] Clinical and epidemiologic studies suggest a strong association between chronic infection, inflammation, and lung cancer. Moreover, cancer-related

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inflammation affects many aspects of malignancy, including the proliferation of malignant cells, angiogenesis, tumor metastasis, and response to chemotherapeutic drugs and hormones.[6]

Electrolyte disturbance is a common symptom in tumor patients, and previous research has found that this condition is associated with poor clinical outcomes in patients.[7] Hyponatremia is commonly seen in cancer patients and is associated with increased mortality and morbidity. Understanding the correct diagnosis and treatment of cancer-associated hyponatremia is critical to achieving better outcomes.[8]

An increased serum albumin and albumin/globulin ratio (AGR) has been reported to be associated with a favorable prognosis for various types of cancer.[9] A low albumin/globulin ratio (AGR) before treatment is associated with poor prognosis in cancer, and AGR can be used as a prognostic marker during cancer treatment.[10]

In China, a retrospective study was conducted in patients with gastric cancer, considering that the pretreatment sodium/globulin (SGO) ratio may be more meaningful in reflecting prognosis than sodium and globulin alone. SGO was found to predict sensitivity to chemotherapy more effectively than sodium or globulin alone and to be an independent and reliable prognostic factor.[11]

In our study, we planned to investigate the role of sodium and globulin levels and ratios at the time of diagnosis in the prognosis prediction of patients diagnosed with lung cancer. It was aimed at determining whether the sodium and globulin ratio at the time of diagnosis was related to the stage, comorbidities, and chemotherapy regimen of the patient diagnosed with lung cancer at the time of diagnosis and to find a cut-off value that could predict the prognosis.

METHODS

Study Design

The study was conducted retrospectively from the patient files and hospital records of patients who were followed up with a diagnosis of lung cancer between January 1, 2015 and January 1, 2021 in Kırıkkale University (KKU) Medical Faculty Hospital, Department of Internal Medicine, and Division of Medical Oncology. The study was initiated with the approval of the medical board, with decision number 2021.06.18. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Participant Selection

Patients who were histopathologically diagnosed with lung cancer in the Department of Medical Oncology, who had evidence of primary tumor and/or metastasis by imaging, who had accessible sodium and globulin levels within the first three months of diagnosis, who were over 18 years of age, and who were followed for at least six months were included in the study. All patients received at least one course of chemotherapy. Patients with conditions that may affect serum sodium and plasma protein levels, such as stage 3 or more chronic kidney disease (CKD), cirrhosis, liver failure, advanced heart failure, central nervous system (CNS) diseases, hypothyroidism, malnutrition, the presence of an active infection, chronic inflammatory bowel disease, nephrotic syndrome, adrenal insufficiency, sepsis, diuretic use, and patients under 18 years of age, were excluded.

Parameters to be Examined

Patient characteristics (age, gender, smoking status, comorbidities, drug use), diagnostic characteristics (date of initial diagnosis, histopathologic subtype, stage, type, and duration of treatment), current health status (presence and date of mortality, presence and date of recurrence), Biochemical parameters (hemoglobin, platelet, leukocyte, C-reactive protein, urea, creatinine, alanine amino transferase, sodium, potassium, glomerular filtration rate, total protein, albumin, globulin, thyroid stimulating hormone, and carcinoembryonic antigen) were evaluated. To evaluate the chemotherapy response of the patients, response evaluation criteria in solid tumors (RECIST 1.1) records kept by the Department of Medical Oncology, Kırıkkale University Medical Faculty Hospital were scanned.

Study Procedure

Patients will be divided into two groups according to their current survival, as follows: (1) deceased; (2) survivors. Patient, diagnostic, and biochemical parameters will be compared between these two groups. Among the parameters analyzed, the relationship between recurrence and mortality, which are associated with prognosis, and serum sodium and globulin levels and sodium/globulin ratios at diagnosis, will be evaluated. In addition, the relationship between CRP/albumin ratio (CAO) and sodium/globulin ratio (SGO) will be evaluated.

Statistical Analysis

The IBM SPSS (Statistical Package for Social Sciences) version 25 program was used. The data were evaluated by the Shapiro-Wilk test and histogram to determine a normal distribution. Numerical variables were presented as mean ± SD or median (min-max), and nominal variables were presented as numbers (percentage) according to their distributional characteristics. In the evaluation of continuous numerical variables between two independent groups, the independent samples t-test was used in the presence of a normal distribution, and the Mann-Whitney U test was used in the absence of a normal distribution. Pearson's chi-square or Fisher's exact test was used for the comparison of categorical variables. Kaplan-Meier test and Cox-regression analysis were used for survival analysis and risk analysis, and the Spearman correlation test was used for correlation analysis. $p<0.05$ was considered significant.

RESULTS

A total of 392 files of 392 patients diagnosed with lung cancer admitted to Kırıkkale University Faculty of Medicine, Department of Oncology, between January 2015 and January 2021 were analyzed. The study data were obtained by a detailed examination of 165 files (144 male and 21 female) selected after excluding patients who did not meet the study criteria. The demographic characteristics of all patients included in the study are shown in Table 1. The mean age of the patients was 62.5±9.1 (mean±SD) years, the median follow-up period was 16.6 (5.3-76.2) months, and 111 patients died during the follow-up period (Table 1).

Table 1. Demographic characteristics of patients with lung cancer at diagnosis (n=165)

Age (Year)	62.5 ± 9.1
Gender n (%) Male Female	 144 (87.3) 21 (12.7)
Histopathology n (%) Adenocarcinoma Squamous cell carcinoma Small cell carcinoma	 76 (46.1) 69 (41.8) 20 (12.1)
Stage n (%) Stage 1 Stage 2 Stage 3 Stage 4	 11 (6.7) 25 (15.2) 58 (35.1) 71 (43)
Survival n (%) Alive Deceased	 54 (32.7) 111 (67.3)
Smoking n (%) Present None	 138 (83.6) 27 (16.4)
Diabetes n(%) Present None	 22 (13.3) 143 (86.7)
Hypertension n (%) Present None	 30 (18.2) 135 (81.8)
Coronary artery disease n (%) Present None	 11 (6.6) 154 (93.4)
Progression n (%) Present None	 123 (74.5) 42 (25.5)
Operation n (%) Present None	 46 (27.8) 119 (72.2)
Follow-up period (month)	16.6 (5.3-76.2)

Data are given as n (%), mean ± standard deviation or median (minimum-maximum).

The laboratory values of the patients with lung cancer included in the study at the time of diagnosis are given in Table 8. Albumin 4.2 mg/dl (2.3-5.1), globulin 2. mg/dl (1.8-4.6) and sodium 140 mEq/L (123-147) levels were within normal limits (Table 2).

Table 2. Laboratory values of patients with lung cancer at the time of diagnosis

Hemoglobin (g/dl)	13.7 (9.5-16.9)
Leukocytes (x 10^3/mm^3)	8.5 (2.4-23.3)
Platelet (x 10^3/mm^3)	273 (111-670)
C-reactive protein (mg/l)	12 (1-43)
Alanine aminotransferase (U/L)	15 (6-150)
Glomerular filtration rate (ml/min/1.73 m^2)	97.2±23.5
Total protein (mg/dl)	7.1±0.6
Albumin (mg/dl)	4.2 (2.3-5.1)
Globulin (mg/dl)	2.9 (1.8-4.6)
Urea (mg/dl)	32 (15-86)
Creatinine (mg/dl)	0.81 (0.4-1.9)
Sodium (mEq/L)	140 (123-147)
Potassium (mEq/L)	4.6±0.4
Sodium/Globulin	48 (27.2-77.7)
Thyroid stimulating hormone (u/U/ml)	1.2 (0.2-4.1)
Carcinoembryonic antigen (ng/ml)	4 (0.7-231)

Data are given as mean ± standard deviation or median (minimum-maximum).

Comparisons of demographic characteristics and laboratory values of surviving and deceased patients are shown in Tables 3 and 4.

Table 3. Demographic characteristics of lung cancer patients at diagnosis according to survival

	Mortality n=111	Survival n=54	p
Age (Year)	63.1 ± 9.6	61.3 ± 7.9	0.237
Male/Female n (%)	98/13 (88.3 /11.7)	46/8 (85.2 /14.8)	0.622
Stage n (%) Stage 1 Stage 2 Stage 3 Stage 4	 1 (9) 13 (11.7) 39 (35.1) 58 (52.3)	 10 (18.5) 12 (22.2) 19 (35.2) 13 (24.1)	**<0.001**
Smoking n (%) Present None	 94 (84.7) 17 (15.3)	 44 (81.5) 10 (18.5)	0.656
Diabetes n (%) Present None	 7 (6.3) 104 (93.7)	 15 (27.8) 39 (72.2)	**<0.001**
Hypertension n (%) Present None	 16 (14.4) 95 (85.6)	 14 (25.9) 40 (74.1)	0.08
Coronary artery disease n (%) Present None	 5 (4.5) 106 (95.5)	 6 (11.1) 48 (88.9)	0.206
Operation (%) Present None	 21 (18.9) 90 (81.1)	 25 (46.3) 29 (53.7)	**<0.001**

Data are presented as n (%), mean ± standard deviation, or median (minimum-maximum). p: Significance level of the difference between living and deceased patients

Table 4. Laboratory values at diagnosis according to survival in patients with lung cancer

	Mortality n=111	Survival n=54	p
Hemoglobin (g/dl)	13.6 (9.5-16.5)	13.7 (10-16.9)	0.48
Leukocytes (x 10^3/mm^3)	8.5 (2.7-23.3)	8.5 (2.4-22.7)	0.503
Platelet (x 10^3 /mm^3)	272 (111-670)	276 (136-600)	0.825
C-reactive protein (mg/L)	15 (1-43)	7 (1-37)	**0.001**
Alanine aminotransferase (U/L)	14 (6-150)	18 (7-103)	**0.049**
Glomerular filtration rate (ml/min/1.73 m^2)	99.8±24.9	93.2±19.9	0.09
Total protein (mg/dl)	7±0.6	7.2±0.5	0.06
Albumin (mg/dl)	4 (2.3-5)	4.3 (2.8-5.1)	**0.001**
Globulin (mg/dl)	3 (1.8-4.6)	2.8 (1.9-3.9)	0.495
Urea (mg/dl)	33 (17-86)	31 (15-80)	0.347
Creatinine (mg/dl)	0.8 (0.4-1.9)	0.9 (0.5-1.6)	0.133
Sodium (mEq/L)	139 (123-147)	140 (133-145)	0.640
Potassium (mEq/L)	4.6±0.5	4.5±0.3	0.234
Thyroid stimulating hormone (u/U/ml)	1.2 (0.2-4.3)	1.1 (0.3-4.1)	0.871
Carcinoembryonic antigen (ng/ml)	4.5 (0.7-183)	3.1 (0.8-231)	**0.001**
Sodium/globulin	47 (27.3-77.7)	49.3 (35.8-76.2)	0.477
C-reactive protein/Albumin	3.9 (0.2-12.9)	1.6 (0.22-10.1)	**<0.001**

Data are presented as n (%), mean ± standard deviation, or median (minimum-maximum). p: Significance level of the difference between living and deceased patients

There was a weak negative correlation between CRP and albumin ratio (CAO) and sodium, and a weak negative correlation between sodium/globulin ratio (SGO) and CAO (r=-0.278, p<0.001; r=-0.415, p<0.001; Figure 1 and Figure 2, respectively).

The Kaplan-Meier curve of cumulative survival for all lung cancer patients during follow-up is shown in Figure 3.

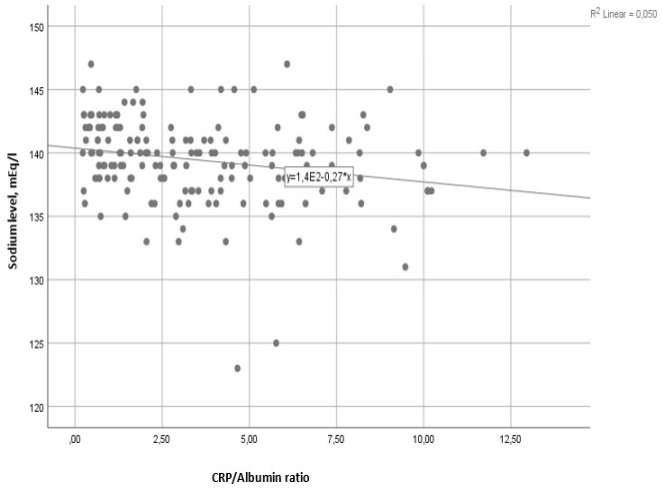

Figure 1. The relationship between serum sodium level and CRP/albumin ratio at diagnosis in patients with lung cancer (r=-0.278 and p<0.001 value)

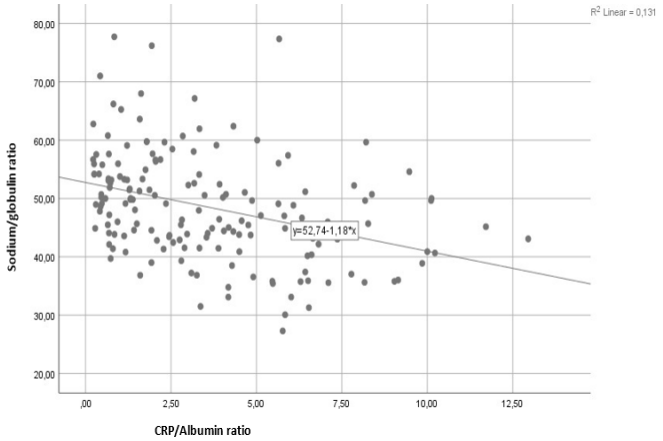

Figure 2. The relationship between serum sodium/globulin ratio and CRP/albumin ratio at diagnosis in patients with lung cancer (r= -0.415 and p<0.001)

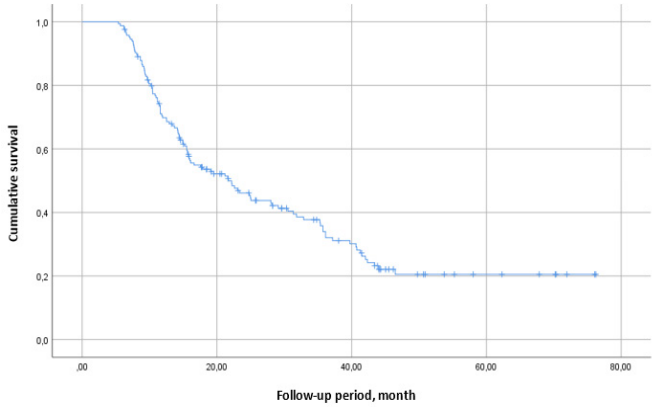

Figure 3. Kaplan-Meier curve of cumulative survival of all lung cancer patients during follow-up

The Kaplan-Meier curve of the cumulative survival of patients with lung cancer during follow-up according to their stage is given in Figure 4. Accordingly, there was a significant difference in survival between the four stages (log rank test p< 0.001).

The laboratory values of the patients with lung cancer included in the study at the time of diagnosis according to progression during follow-up are shown in Tables 5 and 6. Serum sodium, globulin, and sodium/globulin ratio at diagnosis were not significantly different between the two groups (p>0.05).

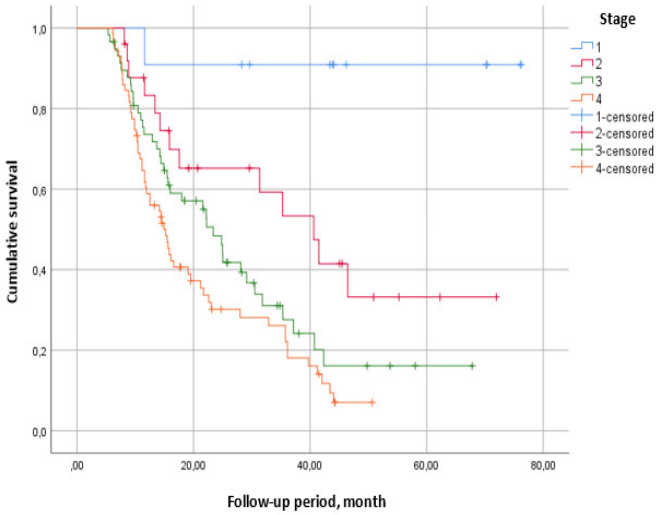

Figure 4. Kaplan-Meier curve of cumulative survival of patients with lung cancer according to stage (log rank test p<0.001)

The CEA value at diagnosis was significantly higher, and the total protein value was lower in patients with progression than those without progression (p<0.05). On the other hand, diabetes mellitus was more common in patients without progression compared to patients with progression, which was statistically significant. The presence of surgery was statistically significant in patients without progression compared to patients with progression. Progression was significantly higher (52.8%) in patients with stage 4 at the time of diagnosis compared to other stages (p<0.001). While the least progression was seen in stage 1 patients (1.6%), patients who did not show progression were mostly stage 3 patients (40.5%) (Table 5, 6).

Table 5. Demographic characteristics of lung cancer patients at diagnosis according to progression status

	Progression n:123	Non-progression n:42	p
Age (Year)	62.7 ± 9.2	61.9 ± 8.4	0.608
Male/Female n (%)	109/14 (88.6 /11.4)	35/7 (83.3 /16.7)	0.423
Stage n (%) Stage 1 Stage 2 Stage 3 Stage 4	 2 (1.6) 15 (12.2) 41 (33.3) 65 (52.8)	 9 (21.4) 10 (23.8) 17 (40.5) 6 (14.3)	**<0.001**
Smoking n (%) Present None	 103 (83.7) 20 (16.3)	 35 (83.3) 7 (16.7)	0.951
Diabetes n (%) Present None	 10 (8.1) 113 (91.9)	 12 (28.6) 30 (71.4)	**0.003**
Hypertension n (%) Present None	 18 (14.6) 105 (85.4)	 12 (28.6) 30 (71.4)	0.06
Coronary artery disease n (%) Present None	 7 (5.7) 116 (94.3)	 4 (9.5) 38 (90.5)	0.474
Operation n (%) Present None	 19 (15.4) 104 (84.6)	 27 (64.3) 15 (35.7)	**<0.001**

Data are given as n (%), mean ± standard deviation or median (minimum-maximum).
p: Significance level of the difference between patients with and without progression

Table 6. Laboratory values at diagnosis according to progression status of patients with lung cancer

	Progression n:123	Non-progression n:42	p
Hemoglobin (g/dl)	13.7 (9.5-16.5)	13.7 (10-16.9)	0.789
Leukocytes (x 10^3/mm^3)	8.38 (2.38-17.6)	8.88 (4.6-23.3)	0.324
Platelet (x 10^3/mm^3)	266 (111-670)	278 (136-600)	0.725
C-reactive protein (mg/L)	13 (1-43)	8.5 (2-37)	0.154
Alanine aminotransferase (U/L)	14 (6-150)	17 (7-103)	0.095
Glomerular filtration rate (ml/min/1.73 m^2)	99.3±23.2	92.8±24	0.130
Total protein (mg/dl)	7±0.5	7.2±0.4	**0.04**
Albumin (mg/dl)	4.16 (2.25-5)	4.17 (3.28-5)	0.497
Globulin (mg/dl)	2.9 (1.8-4.6)	3 (2.3-4.5)	0.284
Urea (mg/dl)	33 (17-86)	32 (15-80)	0.402
Serum creatinine (mg/dl)	0.81 (0.44-1.36)	0.83 (0.58-1.89)	0.476
Sodium (mEq/L)	140 (123-147)	140 (133-145)	0.750
Potassium (mEq/L)	4.6±0.4	4.5±0.3	0.694
Thyroid stimulating hormone (u/U/ml)	1.2 (0.2-4.3)	1.1 (0.3-4.1)	0.551
Carcinoembryonic antigen (ng/ml)	4.2 (0.7-231)	3.3 (0.8-103)	**0.019**
Sodium/globulin	48.9 (27.2-77.7)	46.5 (31.2-60.7)	0.281
C-reactive protein/albumin	3.3 (0.2-12.9)	1.9 (0.4-10.1)	0.137

Data are given as n (%), mean ± standard deviation or median (minimum-maximum).
p: Significance level of the difference between living and deceased patients

The Kaplan-Meier curve of the comparison of progression-free survival of all patients by stage is given in Figure 6. Accordingly, there was a significant difference in progression-free survival between the four stages (log rank test p<0.001).

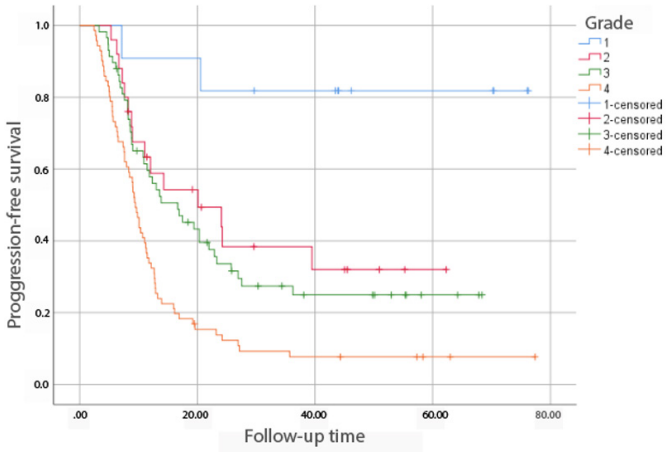

Figure 5. Kaplan-Meier curve of progression-free survival of all lung cancer patients by stage (log rank test p<0.001)

When the factors associated with mortality were analyzed by univariate Cox regression analysis, stage of the disease at diagnosis, presence of surgery, history of diabetes, albumin level, and CRP level were found to be significantly associated with mortality.

In multivariate Cox regression analysis, stage of the disease, patient's diagnosis of diabetes, and CRP level were determined as independent variables in predicting the mortality of patients with lung cancer. In multivariate Cox regression analysis, only the stage of the disease was determined as an independent variable in predicting progression-free survival.

Table 7. Factors affecting mortality in patients with lung cancer (univariate Cox regression analysis, n:165)

	Hazard rate (95% confidence range lower and upper limits)	p
Stage Stage 2-1 Stage 3-2 Stage 4-3	 9.08 (1.18-69.5) 16.36 (2.23-119.69) 23.2 (3.19-168.44)	 **0.034** **0.006** **0.002**
Albumin (mg/dl)	0.618 (0.430-0.889)	**0.009**
Carcinoembryonic antigen (ng/mL)	1.001 (0.996-1.006)	**0.608**
Total protein (mg/dl)	0.82 (0.57-1.16)	**0.265**
Alanine aminotransfer (U/L)	1.005 (0.993-1.019)	**0.409**
Glomerular filtration rate (ml/min/1.73 m^2)	1.005 (0.996-1.014)	**0.256**
C-reactive protein (mg/l)	1.027 (1.010-1.044)	**0.03**
Diabetes mellitus	0.33 (0.15-0.72)	**0.005**
Hypertension	0.67 (0.39-1.15)	**0.15**
Operation presence	0.34 (0.21-0.56)	**<0.001**

Data are given as median (minimum-maximum).
p: Significance level of the factors affecting mortality in univariate Cox regression analysis

In multivariate Cox regression analysis, stage of the disease, patient's diagnosis of diabetes, and CRP level were determined as independent variables in predicting the mortality of patients with lung cancer. In multivariate Cox regression analysis, only the stage of the disease was determined as an independent variable in predicting progression-free survival.

DISCUSSION

In our single-center study, we investigated whether serum sodium, globulin, and sodium/globulin levels at the time of diagnosis play a role in determining survival and progression-free survival in patients diagnosed with lung cancer over a five-year period. In this study, none of the serum sodium and globulin levels or sodium/globulin ratios at the time of diagnosis were found to be effective factors in predicting progression-free survival and mortality in patients diagnosed with lung cancer. The stage of the disease at diagnosis, diabetes, and CRP level were the determinants of mortality. The only factor affecting progression-free survival was the stage of the disease.

Electrolyte disturbance and systemic inflammation are two important causes of poor prognosis in cancer patients. Serum sodium and globulin levels are indicators of electrolyte homeostasis and inflammatory status. These markers have prognostic potential for cancer patients.[11] Patients with cancer often exhibit acid-base and electrolyte disturbances that complicate their treatment and prolong their hospitalization. These abnormalities have multifactorial mechanisms. Both the underlying disease and therapeutic interventions can contribute to their development.[9] Inflammatory cells and the chemokines and cytokines they produce affect tumor tissue by regulating the growth, migration, and differentiation of all cell types in the tumor microenvironment, including neoplastic cells, fibroblasts, and endothelial cells. Later in the tumorigenic process, neoplastic cells also direct inflammatory mechanisms such as selectin-ligand interactions, matrix metalloproteinase (MMP) production, and chemokine functions in favor of neoplastic invasion and metastasis. This may be part of the tumor's attempt to subvert immune cell functions. This sets the stage for tumor development.[12]

In cancer patients, hyponatremia is caused by malignancies, most commonly the syndrome of inappropriate antidiuretic hormone (SIADH) due to SCLC. Hyponatremia can also be triggered by the side effects of anticancer and palliative drugs.[13] The incidence of pretreatment hyponatremia has been found to be high in NSCLC patients as well as in SCLC patients. Hyponatremia is an independent prognostic factor for poor overall survival in lung cancer patients, especially in patients with NSCLC. Hyponatremia appears to be an independent predictor of lower survival in lung cancer patients, especially in patients with NSCLC.[14] These studies have demonstrated the relationship between changes in serum sodium levels during follow-up, mortality, and progression-free survival. In our study, we investigated whether there was a relationship between serum sodium levels at the time of diagnosis and mortality and between sodium levels and progression-free survival in patients diagnosed with lung cancer, and no significant relationship was found.

Abnormal serum albumin has been reported to be closely associated with the progression of many diseases. Moreover, previous studies have shown that decreased albumin levels are associated with an unfavorable prognosis for gastrointestinal cancers, including gastric, colorectal, and pancreatic cancers. In addition, serum globulin has been shown to have a close relationship with immunity and inflammation and to serve as a predictive value in tumor progression.[15] Serum globulin levels are known to be associated with chronic inflammatory diseases. In addition, an excess of inflammatory cells around the tumor has been found to be an accelerator parameter for tumor formation and proliferation.[16] In different studies, elevated globulin levels have been found to have serious adverse effects on cancer patients. Globulin levels have been reported to be associated with prognosis and survival in lung and gastric cancers.[17,18] Albumin and globulin are the main serum proteins and representative indicators of systemic inflammation. The albumin/globulin ratio is mainly used as a clinical indicator of multiple myeloma and other immunoproliferative disorders. Recently, the albumin/globulin ratio has been identified as a predictive value for long-term mortality in patients with nasopharyngeal carcinoma, colorectal cancer, lung cancer, and breast cancer.[19] In our study, serum albumin level at the time of diagnosis appeared to be a predictor of mortality in univariate regression analysis in patients diagnosed with lung cancer but had no effect on mortality in multiple regression analysis. Similarly, serum globulin level at the time of diagnosis were not a determinant of mortality. None of the serum total protein, albumin, or globulin levels at diagnosis were associated with progression-free survival.

The patient population diagnosed with lung cancer mostly consists of patients diagnosed with advanced stages. There are studies supporting this in the literature. Most of the patients' complaints and symptoms are non-specific. Therefore, the majority of patients are diagnosed at an advanced stage. Another 10% of patients are diagnosed incidentally with thoracic imaging without symptoms.[20,21] In our study, the majority of the patient population consisted of advanced-stage patients. A statistically significant correlation was found between the progressive stage of the disease and mortality. In addition, the risk of progression increased significantly as the stage progressed.

Lu et al.[22] examined pre- and postoperative CRP levels in patients diagnosed with gastric cancer and found that high CRP levels were associated with a poor prognosis. This may be related to angiogenesis in proinflammation, resulting in the proliferation of cancer cells and suppression of the immune response. In our study, there was a significant positive correlation between CRP level at the time of diagnosis and mortality in patients diagnosed with lung cancer. This result supports other studies in the literature.

Another parameter that has been widely studied as an inflammatory marker is the CRP/albumin ratio. In a study conducted by Tamagawa et al.[23], the preoperative CRP/albumin ratio was found to be a strong prognostic marker in patients with esophageal cancer. Vujic et al.[24] also showed that the CRP/albumin ratio is a useful prognostic factor in predicting overall survival in patients undergoing pancreatic surgery. In a study by Miyamoto et al.[25] investigating the role of CRP/albumin ratio in predicting short-term survival in patients with and without cancer diagnosis, the CRP/albumin ratio was shown to be a useful and independent factor in predicting short-term survival within two weeks. The possible reason for this is the increase in inflammation in cancer patients, the negative acute phase reactant of albumin, and its decrease due to malnutrition. In our study, a significant difference was found between the CRP/albumin ratio of surviving and deceased patients, and a significant inverse relationship was observed between the CRP/albumin ratio and survival. On the other hand, no significant relationship was found between the CRP/albumin ratio and progression-free survival.

In a study conducted by Zhang et al.[11] on patients with advanced gastric cancer, it was reported that the serum sodium/globulin ratio is an easily applicable marker that can effectively predict sensitivity to chemotherapy before first-line chemotherapy and may also be an independent and reliable prognostic factor to determine progression-free survival and overall survival in patients with advanced gastric cancer. In our study, no statistically significant difference was observed between the serum sodium/globulin ratios of survivors and deceased patients at the time of diagnosis. In addition, no significant correlation was found between progression-free survival and the sodium/globulin ratio.

In our study, only sodium and globulin were analyzed among the values that contribute to electrolyte disturbance and systemic inflammation. Therefore, it is not clear whether SGO is a good prognostic factor. Since our study population consisted of a few patients and was a retrospective study, longer follow-up periods and detection indices will be needed in the future to support these results. However, in our study, there was a weak negative correlation between CRP and albumin ratio (CAO) and sodium, and a weak negative correlation between sodium/globulin ratio and CAO. This correlation between CAO and SGO may be an indication that SGO may be used in prognosis determination in the future.

In a study by Finlayson et al.[26], the mortality rate in patients over 65 years of age who were diagnosed with NSCLC and operated on was found to be lower than in patients operated on for pancreatic and esophageal malignancies. Hoy et al.[27] reported in a study that lung cancer surgery is most applicable to patients with early-stage lung cancer and is the best treatment option for patients with early-stage lung cancer. Howington et al.[28] reported that surgical resection remains the primary and preferred approach in the treatment of stage 1 and 2 NSCLC and that surgical resection reduces perioperative morbidity and mortality and increases long-term survival in patients with

early-stage lung cancer. In our study, although being operated on for lung cancer appeared to be a predictor of mortality and progression-free survival in univariate regression analysis, it was found to have no effect on mortality or progression-free survival in multiple regression analysis.

Recent studies suggest an association between diabetes and lung cancer and claim that diabetes is a risk factor for lung cancer.[29] Diabetes may affect cancer progression and prognosis through various mechanisms. Hyperglycemia has been shown to accelerate tumor metastasis and tumor progression in an animal model of lung cancer through oxidative stress.[30] Sona et al.[31] reported in a study that diabetes may adversely affect the progression of lung cancer and may be a poor prognostic factor for lung cancer. In a multicenter study, it was reported that diabetic patients with lung cancer may have a higher risk of recurrence and more invasive metastatic lung cancer. Diabetes has been shown to increase cancer invasiveness in non-small cell lung cancer through enhancement of epithelial to mesenchymal transition, which plays a key role in local tumor recurrence and metastasis.[32] Singh et al.[33] reported in a study that high insulin levels in response to insulin resistance may have an effect on cancer progression through insulin-like growth factor-1 (IGF-1). On the other hand, there are also studies indicating that diabetes has a positive effect on lung cancer. Since high levels of insulin-like growth factor 1 (IGF-1) can be carcinogenic, one study investigated the role of metformin in reducing IGF-1-mediated tumor formation and showed that metformin reduced IGF-1 levels independently of the adenosine monophosphate-activated protein kinase (AMPK) pathway. In mice treated with metformin, it has been shown that activation of the guanosine triphosphatase (GTPase)-dependent pathway and upregulation of receptor tyrosine kinase activity can significantly reduce tumor formation, independent of the reduction in IGF-1 levels.[34]

Dhillon et al.[35] found that among 409 patients with stage 1 NSCLC with diabetes mellitus, patients receiving metformin had longer survival, and metformin was an independent prognostic factor for NSCLC with diabetes mellitus. Since our patient population is small, our results may be coincidental. This result suggests that more studies are needed to clarify the role of diabetes in lung cancer. Although diabetes appeared to be a predictor of progression-free survival in univariate regression analysis, it had no effect on progression-free survival in multiple regression analysis.

CEA is one of the markers investigated for prognosis prediction in patients diagnosed with lung cancer. Nasralla et al.[36] reported in a meta-analysis of 12 studies in the literature examining the relationship between preoperative carcinoembryonic antigen (CEA) levels and survival in patients with stage 1 NSCLC that higher CEA levels were associated with higher rates of lymph node involvement and higher mortality, and that measuring preoperative CEA in patients with early-stage NSCLC may help identify patients with more advanced disease not detected by CT scan. A meta-analysis of 34 articles published in the literature by Grunnet et al.[37] found that CEA level has prognostic and predictive value in determining the risk of recurrence and mortality in NSCLC. In our study, CEA levels were higher in deceased patients compared to survivors and were not statistically significant. The CEA level of patients with progression was also not statistically significant compared to patients without progression. This is probably because our patient population was limited, the study was retrospective, and the evaluation of lymph node involvement was limited. According to a meta-analysis by Kunutsor et al.[38], there is no strong evidence that ALT has any association with cancer in general, but stratified analysis by geographic location showed an inverse association with ALT level in European populations and a positive association in Asian populations. A pooled analysis of three studies showed a strong positive association between ALT levels and cancers of the digestive tract organs. In our study, the ALT levels of patients who died may have been elevated in advanced-stage patients due to organ metastasis. However, there was no statistically significant correlation between ALT level and mortality or between progression-free survival and ALT.

Study limitations: It was a retrospective study conducted in a single institution with a relatively small number of patients; the majority of patients included in the study were advanced stage patients (which may have affected our results); and in all patients, laboratory parameters were from the pre-treatment period and results were obtained within 3 months from the date of pathologic diagnosis; however, this period was not the same for all patients, which may have affected the study.

The strength of our study: To our knowledge, this is the second study in the literature considering all cancers and the first study on lung cancer.

CONCLUSION

Laboratory parameters are advantageous because they are cheap, easily accessible, and reproducible. Among these laboratory parameters, parameters such as albumin, globulin, total protein, sodium, and CRP can be used for prognosis in cancer patients because they are associated with cancer and inflammation. However, the lack of a precise threshold value with clinical sensitivity and specificity is a problem. Although the sodium/globulin ratio was found to be insignificant in our study, it may be used as a parameter in determining cancer prognosis in the future because it is a new biomarker, significant results were found in previous literature studies, and it was associated with CAO in our study. Since there are not many studies on SGO in the literature, more experimental studies are needed to elucidate the specificity of SGO and its relationship with the etiology of lung cancer.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Kırıkkale University Medical Faculty Clinical Researches Ethics Committee (Date: 01.01.2015/01.01.2021, Decision No: 2021.06.18.).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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